REMARKS

Claims 2, 6, 13, 20-21 and 33-34 remain in the case.

Reconsideration of this Application and entry of the foregoing amendments are requested. Claims 1, 3-5 have been cancelled and claims 2, 6, 20, 21 and 33 have been amended in view of the Office Action and to better define what the Applicants consider their invention, as fully supported by an enabling disclosure. Additional support for the amendments to the claims can be found in the original claims.

Objection relative to the Specification

The Examiner notes that the drawings disclose sequences that are not identified by a sequence identifier. Please note that the specification now indicates in the figure legends the sequence identifiers for each sequences appearing in the drawings. Hence, the sequence of the constructs 1, 2 and 3 were designated by sequence identifiers SEQ ID NOs: 2, 3 and 4 respectively at page 10, lines 9 to 11. The amino acid sequence of Human PHEX is now identified as SEQ ID NO: 1 at page 10, line 13 of the specification.

The Examiner also notes a contradiction between the sequence disclosed in Figure 2 and the recitation at page 29, line 4 of the disclosure. The disclosure refers to a glutamic acid residue at position 582 whereas Figure 2 shows that the glutamic acid residue is at position 581. The disclosure has been modified accordingly.

Claims objections

The Examiner asks that we amend claim 20 to restrict it to elected subject matter, namely PHEX enzymes and variants. Claim 20 has been modified accordingly.

The Examiner requests that we use the full name for PHEX, namely Phosphate regulating gene with homologies to Endopeptidases on the X chromosome in claims. The full name for PHEX, namely "Phosphate Regulating Gene with Homologies to Endopeptidases on the X Chromosome" now appears instead of the term "PHEX" at each first occurrence of the term in the independent claims.

REJECTIONS UNDER 35 U.S.C. § 112 FIRST PARAGRAPH

The Examiner has rejected claims 1-6, 13, 20-21 and 33-34 as failing to comply with the written description requirement under 35 U.S.C. § 112, first paragraph.

REJECTION OF SOLUBLE PHEX VARIANTS

The Examiner considers that the specification fails to disclose the structure of any PHEX other than that of Figure 2 and a PHEX mutant where position 581 is substituted with a valine residue. The Examiner is also of opinion that the disclosure fails to disclose what are the critical structural elements required in a polypeptide for it to possess PHEX function, and which residues could be deleted or substituted to make the PHEX inactive while retaining its ability to bind PHEX ligands.

For that reason, he is of opinion that the disclosure does not provide the necessary support for claims to 1) any PHEX enzyme modified in any way to increase its solubility; 2) any PHEX enzyme modified in any way in the signal/transmembrane region to increase its solubility; and 3) any inactive PHEX enzyme modified in any way to increase its solubility and capable of binding with PHEX ligands. The Examiner alleges that sequence comparison is not a reliable means of identifying variants retaining a protein's function because small amino-acid changes can drastically change the function of the peptide and cites various references to support these points.

Claims 3 to 5 were cancelled to leave only claim 6 specifying that the residue at position 581 according to the numbering used in the sequence of SEQ ID NO: 1 is valine.

With regards to the rejection concerning the lack of support for soluble PHEXs other than that specifically disclosed in Figure 3, although the Applicant respectfully disagrees, claim 1 was cancelled and remaining claims were amended to accelerate prosecution. Broader scope claims will be prosecuted in a continuing application.

In view of the above and foregoing, it is respectfully requested that the Examiner withdraws his rejection of claims 1-6, 13, 20-21 and 33-34 under 35 U.S.C. § 112, first paragraph.

REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1-6, 13, 20-21 and 33-34 have been rejected under 35 U.S.C. § 112, second paragraph as being indefinite.

More particularly, claims 1-2 and their dependent claims 3-6, 20-21 and 33-34 are considered indefinite because it is unclear whether the limitation "comprising a PHEX ectodomain or catalytic part thereof" qualifies both the purified PHEX enzyme and the variants thereof. The Applicants respectfully traverse the rejection as follows. This objection is rendered moot in view of the cancellation of claim 1 and amended claim 2.

Claim 2 is considered indefinite because it is unclear whether the term "eukaryotic host" wherein said host is not a human being excludes human only or also human cells. This objection is rendered moot in view of amended claim 2.

Claims 4-6 are considered indefinite for failing to specify the sequence identifier of the sequence to which these claims refer to. Claims 4 and 5 were amended and claim 6 was amended to specify that position 581 refers to the numbering in SEQ ID NO: 1.

The Applicant wishes to remove any ambiguity as to the reference to SEQ ID NO: 1 in the claims. Reference is made to the sequence of SEQ ID NO: 1 only to indicate more clearly which residues are to be substituted and or deleted to create a soluble PHEX and a soluble inactive PHEX. The present invention is not in any way limited to a particular sequence for PHEX other than that disclosed in SEQ ID NO: 4 which corresponds to the modification or deletion of specific residues in the signal peptide/transmembrane domain. Any PHEX protein modified so as to include the sequence of SEQ ID NO: 4 in the recited position of its signal peptide/transmembrane domain in encompassed by the present invention.

In view of the above and foregoing, it is respectfully requested that the Examiner withdraws his rejection of claims 1-6, 13, 20-21 and 33-34 under 35 U.S.C. § 112, second paragraph.

REJECTION UNDER 35 U.S.C. § 103

Claims 1-2, and 13 have been rejected under 35 U.S.C. §103 as being unpatentable over Guo et al. in view of Lemire et al.

Applicants respectfully traverse the rejection as follows.

The Examiner alleges that since Lemire teaches the expression and secretion of NEP soluble mutants in COS-1 cells, wherein the soluble mutants were obtained by introducing mutations in the signal peptide/transmembrane domain of NEP and that Guo teaches that PHEX has a high homology with NEP, it would have been obvious for POSA at the time of the invention to create a soluble PHEX by modifying its signal peptide/transmembrane domain.

Claim 1 was cancelled. It is respectfully submitted that amended claim 2 does not read on the prior art for the following reasons.

Guo teaches that PHEX has a high homology with NEP. However, this homology is higher in the ectodomains (extracellular domain) of the proteins where their active site is located. In the cytosolic and transmembrane domains of these proteins (a stretch of about 50 amino acid residues at the N-terminal of the proteins), where the mutations were introduced, the homology is barely 20%, and several gaps must be introduced in the sequences to obtain this maximum score. Consistent with this low homology in the N-terminal segment of the proteins, the Applicant's attempt to produce a soluble PHEX using the construct disclosed by Lemire (construct no. 2 (SEQ ID NO: 3) in Figure 1B of the application), failed (see page 18, third paragraph). It is only when 4 residues were removed from the construct no. 2 (SEQ ID NO: 3) as disclosed in Figure 1B to produce construct 3 (SEQ ID NO: 4) in Figure 1B that a soluble PHEX was obtained. The Applicant therefore submits that amended claim 2 and claim 13 which now depends on claim 2 are not suggested by Guo in view of Lemire.

Claims 33 and 34 have been rejected under 35 U.S.C. §103 as being unpatentable over Guo et al. in view of Lemire et al. and Ni et al.

Ni et al. teach an Interleukin-1b converting enzyme (ICE) related protease and a method of finding agents which are functional ligands of the ICE protease such as substrates or inhibitors.

The Examiner alleges that since he considers that the soluble PHEX is obvious in view of Guo and Lemire, the method of identifying PHEX ligands is also obvious. The Applicant respectfully submits that in view of amended claims 2 from which claims 33 and 34 now directly or indirectly depend reciting the soluble PHEX, the method claims are novel and non obvious in view of Guo and Lemire.

The rejections of the original claims are believed to have been overcome by the present remarks and the introduction of new claims. From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such an action is earnestly solicited.

Respectfully submitted,

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